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#10 JRP 9/17/96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Parker, et al.
Serial No.	:	08/432,691
Filed	:	May 2, 1995
For	:	METHODS USEFUL IN ENDOTOXIN BASED PROPHYLAXIS AND THERAPY
Group Art Unit	:	1205
Examiner	:	Jordan, K.

August 22, 1996

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

AMENDMENT - RESPONSE UNDER 37CFR §1.116

S I R:

This response is submitted in reply to the Office Action of May 15, 1996. A one month extension of time is required, and a request therefor, together with fee, accompanies this response.

The allowability of claims 27 and 31 is noted with appreciation. The Examiner has maintained the rejection of the remaining claims, however. The reference relied on is Morton et al. The examiner notes the difference between what is claimed and what is taught; however, she states of this difference:

> "This is not persuasive as applicants have not demonstrated the criticality of the presence of 7% or greater TG. As 2.3% is not seen to differ greatly from 7%, the composition claims remain obvious from the Morton et al. reference."

Reconsideration is requested, for reasons which are set forth herein. It is believed that when the art is taken in proper

context, the reasons why the claimed invention is not obvious will be clear.

Morton et al. did not work with some undefined material; rather, they worked with liposomes. See page 1560 of the full paper, left column, first paragraph:

> "Phosphatidylcholine liposomes of varying TG and/or CE content were prepared, characterized, and used as donors of lipid to, or acceptors of lipid from, LDL."

Liposomes have an art recognized meaning. The record indicates that the Examiner is familiar with the term, but to complete the record, a definition is attached hereto. This definition is taken from deGruyter, Concise Encyclopedia Biochemistry (Berlin, 1988), pages 345-346. At 346, the definition explains that if a liposome is prepared in the presence of water soluble materials, these become entrapped in the resulting liposome. Morton et al. did, in fact, entrap materials such as triglycerides (TG), or cholesteryl ester (CE) in their liposomes.

Liposomes cannot contain unlimited amounts of water soluble materials. They will encapsulate only so much, but not more than this limited amount. An apt analogy is the dissolving of sugar in a fixed volume of water. After a particular point, the sugar settles into the water, but does not dissolve.

For liposomes, the critical point is about 3%. As evidence of this, attached is Handa et al. Biophys. J. 64: 1760-1763 (6/93). The very first sentence states:

> "Some neutral lipids, such as triglycerides (TG) and cholesteryl esters have very low solubility in phospholipid bilayers. The excess amount of the neutral lipid separates from the bilayers and forms droplets in an aqueous medium."

This excess material becomes an emulsion, as Handa reports. The paper goes on to discuss a weight limit of 3.7% for the liposomes. IN other words, regardless of how much neutral lipid is present, only about 3.7% can and will incorporate into a phospholipid bilayer.

What this says is that applicants de facto have an emulsion. What it also says is that the Morton disclosure does, in fact, disclose criticality of a low weight percent for liposomes, because above a certain point, one cannot secure the active material Morton et al. require for their experiments.

Morton et al. are interested in studying the action of lipid transfer protein. LTP must bind to the surface of a donor particle. See page 1561, last paragraph. Liposomes act as the particles. As was pointed out, supra, it would simply not be possible for Morton et al. to have gotten enough neutral lipids into their liposomes to get to what is claimed. The law is quite clear that, if modifying a reference to reach a claimed invention would involve destruction or incorporation of what is described in the reference, the reference does not serve as appropriate prior art. Such would be the case if one sought to modify Morton et al.

It has already been pointed out that Morton et al. recognize this. Please see figure 5, and the accompanying legend. The authors did not even include data at values over 0.75 mole %, because the results were "highly variable." This points to instability in the finished product, i.e., the liposome.

Undoubtedly, it would be theoretically possible to add more neutral lipids to Morton et al.'s liposomes, but what motivation is there to do so? At 0.75 mole %, the data are already so discouraging that they are not even included in the report. This hardly suggests increasing the concentration. Further, as has been pointed out, supra, what was believed possible by the art would have to have been ignored to arrive at what the Examiner has concluded is obvious. In view of this objective evidence, obviousness is not present.

Reconsideration of the rejection, its withdrawal, and allowance of claims 23-31 is believed proper and is urged.

Respectfully submitted,

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